

REMARKS

Applicants have reviewed the Office Action mailed March 27, 2006 (the “Office Action”) and have considered the grounds of rejection presented therein.

Statement of Substance of Interview held August 25, 2006

Applicants’ representative thanks Examiner Miller and Supervisory Examiner Moran (“The Examiners”) for courtesies extended to the undersigned on the occasion of a telephonic interview to discuss rejections of record, on August 25, 2006. Applicants now provide a statement of substance of the interview, as required by MPEP § 713.04.

The rejection of claims 1, 3, and 35 – 62 under 35 USC § 101 was discussed. The Examiners referred the undersigned to the U.S. Patent and Trademark Office (“Office”)’s *Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility*, available on the PTO’s web-site October 26, 2005 and in 1300 O.G. 4, 22 November, 2005 (the “Interim Guidelines”). In particular, the Examiners stated that the Office’s interpretation of the “concrete, useful, and tangible result” requirement for a computer-based invention is that, for a claim to produce a “tangible result” the result of, *e.g.*, a calculation, must be provided to a user, such as by printing, outputting the result to a display, or writing it to a file. (Thus, the Examiners acknowledged that claim 61, reciting output of a structure in protein databank format, would, in fact, be statutory subject matter). The undersigned pointed out that the Interim Guidelines do not recite such a requirement at all. The Examiners responded that they would consider further (written) arguments on this point.

The rejection of claims 1, 35 – 38, 41 – 42, 44, 46, 48, and 51 – 58 under 35 USC § 102(b) was also discussed. The Examiners stated that the reasons for rejecting those claims whose rejections are not supported by particularized rejections in the Office Action were articulated in a previous office action (*e.g.*, Jan. 14, 2005); even though those reasons have not been restated in the most recent action, the Examiners stated that they are assumed still to apply.

With respect to the cited reference, Biggin, the Examiners understood Applicants’ argument that the criteria for anticipation were not met because the claimed invention could not

be pieced together from disparate parts of the reference. The Examiners offered to reconsider this line of reasoning if re-stated in Applicants' forthcoming response.

According to the Examiners, Biggin inherently discloses "identifying" amino acids in a transmembrane region, because it lists transmembrane sequences (*e.g.*, table on p. 169).

According to the Examiners' broadest interpretation, "identifying" need mean no more than simply "pointing out."

The Examiners also stated that they interpreted "constructing" to include "modeling" and that Biggin remains relevant because it discloses "modeling" helices.

The Examiners acknowledged that Biggin does not clearly show "constructing inter-helical loops" under any interpretation of "constructing".

Finally, the Examiners informally stated that the § 102 rejection over Biggin may be withdrawn in a future Action, depending upon Applicants' proffered arguments and upon reconsideration by the Office.

Amendments to the Claims

Claims 1, 3, and 35 – 62 are pending in the instant Application. With the instant amendments, Applicants amend claims 1, 3, 35, 37 – 39, 41 – 44, 46 – 50, and 59, and cancel claim 58. Applicants also introduce new claims 63 and 64.

Claim 1 has been amended to incorporate the limitations of claim 58, now cancelled herein, and to add limitations found in the specification as filed at page 8, paragraph [0016], and in FIG. 4.

Claim 3 is amended to recite a limitation found at page 13, paragraph [0029] of the specification as filed.

Claim 37 has been amended to retain consistent antecedent basis with respect to the instant amendments to claim 1.

Amendments to claim 38 are supported by the specification as filed at page 8, paragraph [0017].

Claims 39, 40 – 43, and 46 are amended to retain consistent antecedent basis with respect to the instant amendments to claim 1.

Claim 49 is amended to recite features of a mixed mode molecular dynamics simulation found in the specification as filed at paragraph [0033], pages 16 – 17.

Claim 50 is amended to recite features of the second molecular dynamics simulation found in the specification as filed at paragraph [0032], pages 15 – 16.

New claim 63, to a computer program product, is supported by the specification as filed, in paragraph [0042], at pages 21 – 22.

New claim 64 is supported by the specification as filed at page 15, paragraph [0031].

All other amendments are merely ministerial in nature, and are supported by the specification as filed as further discussed hereinbelow. Accordingly, no new matter is presented by way of the claim amendments and new claims, and entry thereof is respectfully requested.

REJECTIONS OF THE CLAIMS

Upon entry of the instant amendments, claims 1, 3, 35 – 57, and 59 – 64 are pending in the instant application. As referenced in the Statement of Substance of Interview, discussed hereinabove, Applicants rebut the rejections presented in the Office Action.

Rejections under 35 U.S.C. § 101

The Examiner has rejected claims 1 – 3, and 35 – 62 under 35 U.S.C. § 101 as allegedly being drawn to non-statutory subject matter. Referencing the Interim Guidelines at Section IV.C.2, the Examiner alleges that the instant claims do “not recite steps of producing something that is concrete, useful, and tangible.” Applicants respectfully disagree.

First, although the Examiner has drawn from the Interim Guidelines to frame her rejection, she is respectfully reminded that these Guidelines are, by their own characterization, not the law in the area of processes performed on a computer. (See, *e.g.*, “[t]hese Guidelines do not constitute substantive rule-making and hence do not have the force and effect of law.” Interim Guidelines, at page 2.) On the contrary, the law in this area is controlled by *AT&T Corp. v. Excel Communications, Inc.*, 172 F.3d 1352, 50 USPQ2d 1447 (Fed. Cir. 1999), as well as by

the Federal Circuit's earlier decision in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.* 149 F.3d 1368 (Fed. Cir. 1998). Applicants therefore address the merits of the Examiner's argument, as follows.

The Examiner's explanation for the position adopted is that "[t]he claims do not recite tangible expression (*i.e.*, real-world result) of optimizing the full-atom model, nor any recitation of an actual (*i.e.*, concrete) result in a form useful to one skilled in the art."

Applicants' claims recite a "computer-implemented method for predicting the structure of a membrane-bound protein." In the field of protein structure analysis, where protein structures are notoriously hard to derive experimentally, it is difficult to envisage something more useful than a computer-based method of predicting a structure. The claims recite that the predicted structure is provided as a result of optimizing a full-atom model. One of ordinary skill in the art, who is accustomed to operating computer programs and handling outputs from computer programs would immediately appreciate that a structure provided by a computer implemented method is both useful and real. In the Office Action, the Examiner interprets the supposed requirement for a "tangible expression" as being satisfied by producing a "real-world result". To one of ordinary skill in the art of protein structure modeling, a predicted structure provided by a computer implemented method is very much a real-world result. Such a structure can be displayed, printed, analyzed, stored electronically, and used to solve X-ray diffraction patterns for related structures. Applicants also disagree that a predicted structure is not, according to the Examiner, "an actual (*i.e.*, concrete) result in a form useful to one skilled in the art." Just as a predicted structure is a real-world result, so it is also an actual result in the sense that it can be used by one of ordinary skill in the art. Applications of such structures obtained by Applicants' claimed methods can be found in Applicants' specification as filed, at page 19 (paragraph [0037]).

Applicants now refer the Examiner first to the Interim Guidelines for the Office's own interpretations of the "concrete, useful, and tangible result" requirement for computer-based methods, and second to the applicable case law in this area.

First, the Interim Guidelines state that “[i]n determining whether the claim is for a ‘practical application’, the focus is ... that the final result achieved by the claimed invention is ‘useful, tangible and concrete.’” According to the Interim Guidelines, “[f]or an invention to be ‘useful’ it must satisfy the utility requirement of section 101.” Since the rejection of record does not allege a lack of utility, and since Applicants’ claimed invention does satisfy the utility requirement of 35 U.S.C. § 101 (because it is useful), Applicants need not separately address the requirement that the claim is useful.

The Interim Guidelines further explain that a question of whether an invention produces a “concrete result” arises “when a result cannot be assured.” Neither the rejection of record, nor comments offered by the Examiners during the August 25, 2006 interview, suggest that the results of practicing the instant claims cannot be assured. It thus seems as if the Examiner has conflated the “concrete” and “tangible” requirements into a single ground of rejection, which Applicants now address.

According to the Interim Guidelines, “the tangible requirement does require ... that the process claim must set forth a practical application of that § 101 judicial exception [abstract idea, law of nature, or natural phenomenon] to produce a real-world result.” As discussed hereinabove, Applicants’ claimed method produces a predicted protein structure, something that is undeniably a real-world result in the sphere of protein structure analysis.

Since the Interim Guidelines offer no further guidance, the Examiners, at the August 25, 2006 interview, stated that according to current PTO Interpretations (albeit not enunciated in the Interim Guidelines) a real-world result can only be satisfied by diverting the result of the claimed method (in this case a predicted protein structure) to an output device, such as an electronic display, a printer, or a file stored on a computer-readable medium. Applicants find no such requirement in either the Interim Guidelines or the applicable case law. That such a requirement is not, and was not, intended by the decisions of the Federal Circuit or the U.S. Supreme Court can be seen by analyzing the facts and circumstances of those decisions.

The standard of patentability for computer-based inventions is that set forth in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.* 149 F.3d 1368 (Fed. Cir. 1998):

[W]e hold that the transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces a ‘useful, concrete and tangible result’ – *a final share price momentarily fixed for recording and reporting purposes and even accepted and relied upon by regulatory authorities and in subsequent trades.*” (emphasis added).

State Street Bank concerned a patent for a data processing system used in the financial services industry, the validity of whose claims was upheld. The claim in *State Street Bank* recited no outputting step or means, but did recite a “storage means for storing data on a storage medium.”

There are two consequences of the Federal Circuit’s opinion in *State Street Bank*. First, it is not the outputting a result of a calculation in a particular form that is a pre-requisite to finding a claimed process statutory, but instead it is the ability of others to access the result. Second, the result does not have to be preserved in a permanent manner. Neither of these consequences dictates that an Applicant’s claimed method must recite an outputting step.

Furthermore, it is not the form of the manipulations embodied in the claims, but the outcome of their application, upon which patentability is judged. The court in *State Street Bank* went on to conclude that “[t]he question of whether a claim encompasses statutory subject matter should not focus on which of the four categories of subject matter a claim is directed to ... but rather on the essential characteristics of the subject matter, in particular, its practical utility” and not how or whether the claim produces an output.

It also seems implausible that the Federal Circuit could have intended that, on the one hand, the momentary fixation of a final share price in a computer system can render a claimed process useful, whereas on the other hand the momentary fixation of a predicted protein structure does not. In essence, it is difficult to see how the result of Applicants’ claimed method is any less “useful, concrete and tangible” than that of transiently recording a share price. A share may have a paper form, and its price, although an abstract quantity, is one which may be practically manipulated by a computing machine; similarly a protein is a physical object whose structural

coordinates find a practical realization when stored and manipulated in numerical form on a computer.

Similarly, *AT&T* affirms the patentability of “a mathematical algorithm, [that] may be an integral part of patentable subject matter such as a machine or process if the claimed invention as a whole is applied in a ‘useful’ manner.” *AT&T* at 1358. According to *AT&T*, a mathematical algorithm is patentable subject matter to the extent that it produces a “useful, concrete, or tangible result”. In deciding the patentability of the claimed invention in *AT&T*, the Federal Circuit concluded that an algorithm for use in telecommunications did indeed produce such a result. In *AT&T*, the claimed method “generates a message record for an interexchange call” using a specific algorithm. In the algorithm, an indicator, whose value is determined by a Boolean principle, is used to determine the rate at which a long-distance telephone is charged, depending upon which exchange carrier the call is routed over. The court found that “[t]he PIC indicator represents information about the call recipient’s PIC, a useful, non-abstract result that facilitates differential billing of long-distance calls made by an IXC’s subscriber.” *Id.* at 1358. The court noted that, in accordance with one of its earlier decisions, “[t]hat the product is numerical is not a criterion of whether the claim is directed to statutory subject matter.” *Id.* at 1358.

In particular, according to *AT&T*, “the mere fact that a claimed invention involves inputting numbers, calculating numbers, outputting numbers, and storing numbers, in and of itself, would not render it non-statutory subject matter, unless, of course, its operation does not produce a ‘useful, concrete and tangible result.’” *Id.* at 1359, citing to *State Street Bank*. Thus, the patentability inquiry always reverts to the nature of the application of the claimed process, and not to how or in what form it is achieved.

Applicants respectfully point out that the claim in *AT&T* was for an automated method that did not require the act of placing a telephone call, or routing a telephone call. The claim merely recited “generating a message record for an inter-exchange call” and thus was purely numerical in both its action and result. This is significant because it shows that the output that the Office requires in the claim itself is illusory at best. The practical application upon which the

patentability of the *AT&T* claim is founded is that the computed steps may be used within the telecommunications industry; the calculated quantity had meaning when ascertaining the appropriate carrier to charge when connecting a long-distance telephone call.

Similarly, Applicants' claims harness a mathematical algorithm to produce a predicted protein structure. Such an application also clearly produces a useful, concrete, and tangible result, within the terms of the law, because the data that is being manipulated corresponds to physical quantities (molecular structural data) that have independent meaning outside of the computer, and because the end result of the process is a transformed set of molecular data that renders drug design — practical activities carried out by scientists — more straightforward.

In summary, whether or not Applicant's claimed invention directs output to, *e.g.*, a printer, does not settle the question of whether it is statutory subject matter. Specifically, the Examiner's reading of the terms "concrete, tangible, and useful" as requiring an output directed to a user is simply not the law. Applicant reminds the Examiner again that the "inquiry here focuses on whether the mathematical algorithm is applied in a practical manner to produce a useful result" *AT&T* at 1360, and not whether it directs its output to a device.

Rejections under 35 U.S.C. § 112 (¶ 1)

The Examiner has stated that claims 1, 3, and 35 – 62 stand rejected under 35 U.S.C. § 112 (first paragraph) as allegedly reciting subject matter that was not described in the specification in such a way as to convey that the inventors had possession of the invention at the time the application was filed. Applicants respectfully traverse the rejection as it applies to claims 3 and 35, and request that the rejection of claims 1, and 36 – 62 be removed because it cannot apply to such claims.

First, Applicants note that no rejection has been articulated under 35 U.S.C. § 112 (first paragraph) for claim 1. Applicants therefore assume that the rejections under this section neither apply to claim 1, nor to any claim which depends from claim 1 for which a separate rejection has not been articulated (*i.e.*, claims 36 – 62).

Applicants address the rejections of claims 3 and 35, as follows.

With respect to claim 3, the Examiner alleges that Applicants' introduction of the phrase "one or more of" is new matter. Although Applicants believe that the specification, in particular the second half of paragraph [0015] on page 7, can be read inclusively such that not all of the enumerated steps ("constructing", "calculating", and "optimizing") are required to be performed when constructing helices for the transmembrane regions, in the interests of expediting prosecution, Applicants delete the offending text from claim 3 with the amendment presented herein.

In claim 35, the Examiner objected to the clause "one or more of" and the following list of steps, as not being part of "optimizing a helix bundle configuration". In response, Applicants delete "one or more of", and refer the Examiner to the foregoing sentiments in connection with claim 3.

Additionally, Applicants amend claim 35 to delete "assembling a helix bundle including each of the set of helices".

Accordingly, Applicants respectfully request that the rejections of claims 1, 3, and 35 – 62 under 35 U.S.C. § 112 (first paragraph) be removed.

Rejections under 35 U.S.C. § 112 (¶ 2)

The Examiner has rejected claims 1, 3, and 35 – 62 under 35 U.S.C. § 112 (second paragraph) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse the rejection.

The Examiner has objected to the clause "thereby providing" as it applies to the predicted structure as recited in claim 1. Applicants respectfully disagree. The use of a "thereby" clause in the last step of a claim is widespread claiming practice, particularly where it is desired to tie the result of a claimed method to a stated objective in the claim's preamble. Nothing about the use of such a clause in instant claim 1 has introduced any lack of clarity. Nevertheless, in an effort to accommodate the Examiner at least in part, Applicants amend claim 1 herein to replace "thereby providing" with "to provide" in the expectation that this may provide the clarity sought

by the Examiner. The last step of claim 1, as amended herein, is therefore a step of “optimizing the full-atom model”, a step which results in a “predicted structure” as set forth in the preamble to the claim.

Applicants, accordingly, respectfully submit that the amendment to claim 1 renders the rejection under 35 U.S.C. § 112 (second paragraph) moot, and request that it be removed.

Rejections under 35 U.S.C. § 102(b)

Claims 1, 36-38, 41-42, 44-46, 48, and 51-58 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by a review article by Biggin and Sansom, *Biophysical Chemistry*, 76:161-183 (1999) (hereinafter “Biggin”). Applicants respectfully traverse the rejection because Biggin does not disclose each and every element of the recited claims.

As recited in Applicants’ claims as amended herein, Applicants’ invention provides a method for predicting the structure of membrane bound protein, comprising several steps, including: constructing helices in transmembrane regions and inter-helical loops therebetween, obtaining an optimized structure for each of the two or more helices, assembling the optimized structures of the two or more helices into a helix bundle, optimizing a helix bundle configuration for the set of helices using a first molecular dynamics simulation, and optimizing the full-atom model using a second molecular dynamics simulation.

Applicants remind the Examiner that “a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Biggin does not disclose at least constructing inter-helical loops between trans-membrane helices.

First, Applicants’ claim 1 recites “after optimizing the helix bundle configuration, constructing one or more inter-helical loops to generate a full-atom model of the membrane-bound protein”. Such a step cannot be found in the teachings of Biggin. During the August 25, 2006 Interview, the Examiners referred the undersigned to Biggin, at the bottom of the right hand column on page 179, for a reference to inter-helix loops (“[f]luctuations in the structure

over the course of the simulation were greater for the inter-helix loops than for the TM helices”). This statement and a similar statement on p. 178 (left hand column) are the only references to inter-helix loops in Biggin, and do not describe a method of constructing inter-helix loops, as required by Applicants’ claims. The statements in Biggin are merely an observation that, based on comparisons of inter-helix loops and TM helices during a simulation, the inter-helix loops showed greater variability than the transmembrane helices. Accordingly, Biggin does not provide a disclosure that anticipates Applicants’ claimed invention, at least because it does not disclose a step of constructing inter-helical loops.

Applicants now also further respectfully submit that Biggin does not disclose separate steps of “obtaining an optimized structure for each of the two or more helices” and “assembling the optimized structures of the two or more helices into a helix bundle”, as recited in amended claim 1. Accordingly, at least three steps recited in claim 1 are not found in Biggin.

Should the Office disagree with this view of Biggin, Applicants’ respectfully reiterate views expressed in their January 19, 2006 response, that, notwithstanding the reference to inter-helix loops in Biggin, the Office’s findings are insufficient to meet the legal requirements of anticipation. In particular, “[t]he identical invention must be shown in as complete detail as is contained in the ... claim.” *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); see also MPEP § 2131. Thus, the claim elements must be arranged in the reference as required by the claim (though this is not an *ipsissimis verbis* test, *i.e.*, identity of terminology is not required), *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). Applicants respectfully point out that Biggin does not describe Applicants’ invention as recited in the claims.

As set forth in Applicants’ specification, Applicants’ “invention provides a computational hierarchical strategy for predicting the structure of certain transmembrane proteins such as G-protein coupled receptor” (Specification at page 11, ¶ [0026]). In particular, Applicants’ invention comprises at least two separately applied molecular dynamics simulations: a (‘coarse-

grained') simulation of a helix bundle configuration; and a ('fine-grained') optimization of a full-atom model.

By contrast, Biggin reviews two distinct classes of simulations, mean field simulations, and all-atom molecular dynamics simulations (both of which are applied to mechanisms of insertion of transmembrane helices into bilayers), but does not describe a method in which two molecular dynamics simulations are applied, consecutively, to different parts of a protein structure prediction problem. In particular, Biggin does not disclose separate and consecutive steps of at least optimizing a helix bundle configuration, and optimizing a full-atom model. Accordingly, Biggin does not anticipate Applicants' claims because to derive Applicants' invention from Biggin it is necessary to rearrange disparate, unconnected, aspects of Biggin's disclosure in a manner clearly not taught by Biggin (as well as to insert steps not explicitly taught by Biggin).

In conclusion, Biggin does not anticipate claim 1 and, accordingly, Applicants respectfully request that the rejection of record be removed.

Rejections of claims 36-38, 41, 42, 44-46, 48, and 51-58

As argued hereinabove, Biggin does not anticipate claim 1. Therefore Biggin cannot also anticipate any claim that depends – directly or indirectly – from claim 1.

Applicants assert that the record suggests that specifically articulated claim rejections under 35 U.S.C. § 102(b) remain in effect only as to claims 1, 37, 38, and 41. At the August 25, 2006 Interview, the Examiners stated that Applicant should refer to previous Office Actions for a recitation of specific grounds of rejection of dependent claims not articulated in the March 27, 2006 Office Action. Yet, the March 27, 2006 Office Action clearly states "[r]ejections and/or objections not reiterated from previous office actions are hereby *withdrawn*." (Office Action, at page 2, emphasis added.) Accordingly, Applicants think that it is fair to assume, from the written record, that the rejection under 35 USC § 102(b) over Biggin only applies to claims 1, 37, 38, and 41.

As stated hereinabove, since Biggin does not anticipate claim 1, it cannot anticipate any claim depending therefrom. Nevertheless, in the interests of expediting prosecution Applicants address the individual grounds of rejection of claim 38 because a further specific teaching alleged by the Examiner to be found in Biggin is clearly not so present. Claim 38 recites “determining a periodicity of hydrophobic residues.” The Office references Biggin (p. 166, left column) for “periodicity of proline residue”. However, Applicants see no such teaching in Biggin. While Biggin does reference proline in the passage called out, there is no reference to periodicity, as required by the claim. Thus, Biggin does not teach at least one element recited in claim 38.

Accordingly, Applicants respectfully request that the rejection of claims 1, 36-38, 41, 42, 44-46, 48, and 51-58 under 35 U.S.C. § 102(b) over Biggin should be removed.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 3, 39, 40, 45, 47, 49, and 50, under 35 U.S.C. § 103(a) as allegedly being obvious over Biggin in view of one or more other cited references.

The U.S. Patent and Trademark Office (“PTO”) bears the burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993). To establish a *prima facie* case, the PTO must satisfy three basic criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the reference teachings in the manner suggested by the PTO. *In re Rouffet*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). Second, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the PTO would be successful. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Finally, the prior art reference, or references when combined, must teach or suggest each and every limitation of the claimed invention. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). The teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in

the prior art, not in the Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). If any one of these criteria is not met, *prima facie* obviousness is not established.

Each of the rejections reiterates the rationale according to which claim 1 was rejected under 35 U.S.C. § 102(b) over Biggin, and where a recitation in a particular claim is not to be found in Biggin, utilizes one or more secondary references as support.

Therefore, and in the interests of brevity, Applicants preface their rebuttal of all rejections with a statement of reasons why Biggin — on its own — does not provide sufficient teachings to render Applicants' claimed invention obvious.

As stated hereinabove, Biggin reviews methods of simulating interactions between α -helices and lipid bilayers. To that end, Biggin describes and contrasts two categories of molecular dynamics simulations, 'mean field' and 'all-atom' approaches, that have been applied to such interactions. Biggin fails to teach or suggest, however, a simulation protocol as recited in Applicants' claims. In particular, Biggin fails to teach or suggest the consecutive application of two or more molecular dynamics simulations to different parts of a multi-helix system, and Biggin fails to teach a recipe of steps including, at least, optimizing individual helices, assembling such helices into a bundle, and constructing inter-helical loops between helices. Accordingly, in order to sustain a *prima facie* case, the Office must show that the teachings missing from Biggin are found in one or more other cited references and that a motivation to combine the respective teachings and to modify Biggin existed in the art, prior to Applicants' invention. This much, at least, the Office has not shown as demonstrated by Applicants' remarks hereinbelow.

It is therefore unnecessary, in responding to each rejection, for Applicants to address considerations of motivation to combine the references and the alleged expectation of success associated with such a combination.

Rejection over Biggin in view of Mathiowetz and Sansom

The Examiner has rejected claims 39, 40, and 50 under 35 U.S.C. § 103(a) as allegedly being obvious over Biggin in view of Mathiowetz, *et al.*, *Proteins: Structure, Function, and*

Genetics, 20:227-247 (1994), (“Mathiowetz”), and further in view of Sansom *Biophys. J.*, 68:1295-1310, (1995) (“Sansom”). Applicants respectfully traverse the rejection, at least because the cited references do not, either alone or in combination, teach every element of the claims.

Applicants first point out that Sansom is not of record in the instant application. It has neither been provided by Applicants to the Examiner in conjunction with one of the Information Disclosure Statements previously filed, nor has it previously been cited by the PTO. Furthermore, a copy of Sansom was not provided with the March 27, 2006 Office Action. Applicants have obtained their own copy of Sansom for the purposes of responding to the instant rejection. Nevertheless, Applicants respectfully request that the Examiner list Sansom on PTO Form 894 at such time as she next issues an action in the instant application so that it may properly be made of record.

Claims 39, and 40 recite a method of predicting a protein structure wherein a torsional molecular dynamics method is applied to obtaining an optimized structure for each of two or more helices. Claim 50 recites a method of predicting a protein structure wherein a torsional molecular dynamics method is applied to optimizing a full-atom model of a membrane-bound protein, and wherein cell multipole methods are used to calculate nonbond forces.

The essence of the Examiner’s rejection is that: Biggin (allegedly) teaches Applicants’ method as recited in claim 1; Mathiowetz teaches the use of torsional molecular dynamics (specifically the Newton-Euler Inverse Mass Operator method) and the cell multipole method in protein simulation; and that one of ordinary skill in the art would have been motivated to combine the respective teachings to “improve simulations of large proteins”. Sansom is cited to support the proposition that the (Ala)₉ systems to which Mathiowetz applies his methods are themselves used as a model for simulating structures of transmembrane protein helices.¹

¹ Applicants note that Mathiowetz discusses application to the peptide (Ala)₉ but does not suggest that this peptide adopts a helical configuration. Sansom uses (Ala)₂₀, a peptide that is more than twice as long, to simulate α -helices.

However, as discussed hereinabove, Biggin does not teach each and every element of claim 1. Neither Mathiowetz nor Sansom provides the elements of claim 1 not taught by Biggin. Thus, neither Mathiowetz nor Sansom teach a protocol in which molecular dynamics is applied *successively* to different components of a protein structure. In particular, Mathiowetz simply commends use of NEIMO for simulation of “very large proteins and polymers” but without suggesting a protocol in which those molecules are addressed hierarchically as required by Applicants’ claims; Sansom uses simulated annealing via restrained molecular dynamics to “undertake a systematic investigation of possible structures for 7TM bundles” (Sansom, p. 1296, left hand col.) but again, without suggesting a hierarchical approach.

In summary, even though Mathiowetz provides certain elements of claims 39, 40, 50 not taught or disclosed by Biggin, these claims are not obvious over a combination of Biggin, Mathiowetz, and Sansom, at least because of the deficiencies of Biggin alone. Accordingly, Applicants respectfully request that the rejection of claims 39, 40, and 50 under 35 U.S.C. § 103(a) be removed.

Rejection over Biggin in view of Mayo

The Examiner has rejected claim 47 under 35 U.S.C. § 103(a) as allegedly being obvious over Biggin in view of Mayo, *et al.*, *J. Phys. Chem.*, 94:8897-8909 (1990) (“Mayo”). Applicants respectfully traverse the rejection, at least because the combination of references does not teach or disclose every element of the invention.

In the first instance, as has been established hereinabove, Biggin does not teach each and every element of claim 1, from which claim 47 depends. Mayo does not provide the deficiencies of Biggin; specifically, Mayo does not teach or disclose a hierarchical protocol, comprising successive molecular dynamics simulations applied to different components of a protein structure. Instead, Mayo discloses parameters for a molecular mechanics force field. Accordingly, for at least this reason and notwithstanding the additional teachings of Mayo, the rejected claims are not obvious over a combination of Biggin and Mayo. Applicants respectfully request that the rejection of record be removed.

Rejection over Biggin in view of Benner

The Examiner has rejected claim 3 under 35 U.S.C. § 103(a) as allegedly being obvious over Biggin in view of U.S. Patent No. 5,958,784 to Benner (“Benner”). Applicants respectfully traverse the rejection, at least because the combination of references does not teach or disclose every element of the invention.

Again, as has been established hereinabove, Biggin does not teach each and every element of claim 1, from which claim 3 depends. Benner does not provide the deficiencies of Biggin; specifically, Benner does not teach or disclose a hierarchical protocol comprising successive molecular dynamics simulations applied to different components of a protein structure. On the contrary, Benner is absolutely silent as to molecular dynamics and simulations generally.

In fact, Benner discloses an *empirical* method of predicting secondary and tertiary structures based on primary sequence information. In this respect, at least, the combination of Benner with Biggin is inapposite. Thus, according to the Examiner, Benner discloses canonical helices (Benner col. 16)² thereby allegedly providing an element of claim 3 not disclosed by Biggin. However, as a closer reading of Benner reveals, “canonical” in the sense used by Benner refers to a provisional assignment of an element of secondary structure based on certain empirical rules as derived from the primary sequence. In contrast, the canonical structures of Applicants’ invention are three-dimensional helical structures.

Accordingly, for at least the foregoing reasons, claim 3 is not obvious over a combination of Biggin and Benner, and Applicants respectfully request that the rejection of record be removed.

Rejection over Biggin in view of Turner

The Examiner has rejected claim 45 under 35 U.S.C. § 103(a) as allegedly being obvious over Biggin in view of U.S. Patent No. 5,424,963 to Turner (“Turner”). Applicants respectfully

² The Examiner also refers to “Albert, col. 16, lines 25-63” (March 27, 2006 Office Action, page 14, 2nd line from the bottom of the page), but Applicants assume that this is a clerical error, as no other reference to a publication by Albert is of record.

traverse the rejection, at least because the combination of references does not teach or disclose every element of the Applicants' invention.

Again, as has been established hereinabove, Biggin does not teach each and every element of claim 1, from which claim 45 depends. Turner does not provide the deficiencies of Biggin; specifically, Turner does not teach or disclose a hierarchical protocol comprising successive molecular dynamics simulations applied to different components of a protein structure.

Accordingly, for at least the foregoing reasons, claim 45 is not obvious over a combination of Biggin and Turner. Applicants respectfully request that the rejection of record be removed.

Rejection of claim 49 over Biggin in view of Mathiowetz, Sansom and Turner

The Examiner has rejected claim 49 under 35 U.S.C. § 103(a) as allegedly being obvious over Biggin in view of Mathiowetz, Sansom, and further in view of Turner. Applicants respectfully traverse the rejection, at least because the combination of references does not teach or disclose every element of the claim, as amended herein.

Again, as has been established hereinabove, Biggin does not teach each and every element of claim 1, from which claim 49 depends. Additionally, Applicants respectfully submit that the instant amendments to claim 49 render the rejection of record moot. In addition to not providing every element of claim 1, the combination of references does not teach or suggest every element of claim 49 as amended herein.

Accordingly, for at least the foregoing reasons, claim 49 is not obvious over a combination of Biggin, Mathiowetz, Sansom, and Turner. Applicants respectfully request that the rejection of record be removed.

In summary, claims 3, 39, 40, 45, 47, 49, and 50 are not obvious over Biggin in combination with any of the other cited references, and Applicants respectfully submit that the rejections of record under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the subject application is in good and proper order for allowance. Withdrawal of the Examiner's rejections and early notification to this effect are earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 839-5070.

No fee is believed owed in connection with filing of this amendment and response other than the fee associated with the petition for extension of time. However, should the Commissioner determine otherwise, the Commissioner is authorized to charge any underpayment or credit any overpayment to Fish & Richardson P.C. Deposit Account No. 06-1050 (ref. No. 06618-606001) for the appropriate amount. A copy of this sheet is attached.

Date: September 27, 2006

Respectfully submitted,

Richard G. A. Bone
Richard G. A. Bone
Reg. No. 56,637

Fish & Richardson P.C.
500 Arguello Street, Suite 500
Redwood City, California 94063
Telephone: (650) 839-5070
Facsimile: (650) 839-5071



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Application No. 09/816,755	Filing Date March 23, 2001	Attorney/Secretary Init RGB/efd	
Title of the Invention METHOD AND APPARATUS FOR PREDICTING STRUCTURE OF TRANSMEMBRANE PROTEINS			
Applicant Nagarajan Vaidehi, et al.			
Client Reference No. CIT 3191			
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